Building a network of ADPKD reference centres across Europe: the EuroCYST initiative

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Abstract: BACKGROUND: Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic inherited kidney disease, affecting an estimated 600 000 individuals in Europe. The disease is characterized by age-dependent development of a multiple cysts in the kidneys, ultimately leading to end-stage renal failure and the need of renal replacement therapy in the majority of patients, typically by the fifth or sixth decade of life. The variable disease course, even within the same family, remains largely unexplained. Similarly, assessing disease severity and prognosis in an individual with ADPKD remains difficult. Epidemiological studies are limited due to the fragmentation of ADPKD research in Europe. METHODS: The EuroCYST initiative aims: (i) to harmonize and develop common standards for ADPKD research by starting a collaborative effort to build a network of ADPKD reference centres across Europe and (ii) to establish a multicentric observational cohort of ADPKD patients. This cohort will be used to study factors influencing the rate of disease progression, disease modifiers, disease stage-specific morbidity and mortality, health economic issues and to identify predictive disease progression markers. Overall, 1100 patients will be enrolled in 14 study sites across Europe. Patients will be prospectively followed for at least 3 years. Eligible patients will not have participated in a pharmaceutical clinical trial 1 year before enrollment, have clinically proven ADPKD, an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 m(2) and above, and be able to provide written informed consent. The baseline visit will include a physical examination and collection of blood, urine and DNA for biomarker and genetic studies. In addition, all participants will be asked to complete questionnaires detailing self-reported health status, quality of life, socioeconomic status, health-care use and reproductive planning. All subjects will undergo annual follow-up. A magnetic resonance imaging (MRI) scan will be carried out at baseline, and patients are encouraged to undergo a second MRI at 3-year follow-up for qualitative and quantitative kidney and liver assessments. CONCLUSIONS: The ADPKD reference centre network across Europe and the observational cohort study will enable European ADPKD researchers to gain insights into the natural history, heterogeneity and associated complications of the disease as well as how it affects the lives of patients across Europe.

DOI: https://doi.org/10.1093/ndt/gfu091

Originally published at:
Petzold, Katja; Gansevoort, Ron T; Ong, Albert C M; Devuyst, Olivier; Rotar, Laura; Eckardt, Kai-Uwe; Köttgen, Anna; Pirson, Yves; Remuzzi, Giuseppe; Sandford, Richard; Tesar, Vladimir; Ecder, Tevfik; Chaveau, Dominique; Torra, Roser; Budde, Klemens; Le Meur, Yannick; Wüthrich, Rudolf P; Serra, Andreas L (2014). Building a network of ADPKD reference centres across Europe: the EuroCYST initiative. Nephrology, Dialysis, Transplantation, 29 Suppl:iv26-iv32.
DOI: https://doi.org/10.1093/ndt/gfu091

Building a network of ADPKD Reference Centers across Europe: The EuroCYST Initiative

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Running title: EuroCYST

Keywords: ADPKD, biomarker, cohort, EuroCYST, prognosis, risk factors

Word count abstract: 364
Word count body: 3664

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Summary: The EuroCYST Initiative aims to build a network of ADPKD reference centers across Europe and to establish a large-scale observational cohort of ADPKD patients for the purpose of studying the pathogenesis, rate of disease progression, progression rate modifiers, disease stage specific morbidity, mortality, health economic issues and the predictive value of biomarkers in ADPKD. Overall 1,100 patients will be enrolled in 14 study sites across Europe and will be followed up for at least three years. The ADPKD reference center network across Europe and the observational cohort study will enable European ADPKD researchers to gain insight into the natural history, heterogeneity and associated complications of the disease as well as how it affects the lives of patients across Europe.

Abstract

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic inherited kidney disease, affecting an estimated 600,000 individuals in Europe. The disease is characterized by age dependent development of a multitude of cysts in the kidneys, ultimately leading to end-stage renal failure and the need of renal replacement therapy in the majority of patients, typically by the 5^{th} or 6^{th} decade of life. The variable disease course, even within the same family, remains largely unexplained. Similarly, assessing disease severity and prognosis in an individual with ADPKD remains difficult. Epidemiologic studies are limited due to the fragmentation of ADPKD research in Europe.

Methods: The EuroCYST Initiative aims (i) to harmonize and develop common standards for ADPKD research by starting a collaborative effort to build a network of ADPKD reference centers across Europe; and (ii) to establish a multicentric observational cohort of ADPKD patients. This cohort will be used to study factors influencing the rate of disease progression, disease modifiers, disease stage specific morbidity and mortality, health economic issues and to identify predictive disease progression markers. Overall 1,100 patients will be enrolled in 14 study sites across Europe. Patients will be followed prospectively for at least three years. Eligible patients will not have participated in a pharmaceutical clinical trial one year before enrollment, have clinical proven ADPKD, an estimated glomerular filtration rate (eGFR) of 30 ml/min/1.73m^2 and above and be able to provide written informed consent. The baseline visit will include a physical examination and collection of blood, urine and DNA for biomarker and genetic studies. In addition, all participants will be asked to complete questionnaires detailing self-reported health status, quality of life, socioeconomic status, healthcare use and reproductive planning. All subjects will undergo annual follow-up. A magnetic resonance imaging (MRI) scan will be carried out at baseline and patients are

encouraged to undergo a second MRI at 3 years follow-up for qualitative and quantitative kidney and liver assessments.

Conclusion: The ADPKD reference center network across Europe and the observational cohort study will enable European ADPKD researchers to gain insight into the natural history, heterogeneity and associated complications of the disease as well as how it affects the lives of patients across Europe.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common monogenic genetic diseases, affecting approximately 1 in 1,000 live births, i.e. around 600,000 individuals in Europe.[1] The disease is characterized by the development of multiple cysts in both kidneys and by potentially serious complications.[2] Disease manifestations impairing quality of life include hypertension, chronic pain, intracranial aneurysms, abdominal hernias, hematuria, urinary tract infection, and kidney stones. Kidney function is often preserved up to the age of 40, but subsequently glomerular filtration rate (GFR) decreases and often leading to end-stage renal disease (ESRD).[3] However there is wide variability between subjects in disease course, even within families that share the same mutation, with some patients never reaching ESRD.

ADPKD represents a major burden for public health in the EU, estimated at €1.6 billion annually for direct medical costs related to renal replacement therapy.[4] This figure is an underestimate of the true economic burden, because it does not take into account costs related to co-morbidities which frequently occur in patients with impaired kidney function and the loss of income generation that is often observed in subjects with later stage kidney disease. Research on prevention of ADPKD related complications could therefore offer a tremendous return on investment.

At present there are no approved disease modifying treatments available for ADPKD. Intensive basic research during the last three decades has contributed to a clearer understanding of the basic pathophysiological processes that lead to renal cyst formation in subjects affected by ADPKD with definition of novel therapeutic targets.[5,6] In animal studies some of the treatments directed at these targets, such as mammalian target of rapamycin (mTOR) inhibitors, somatostatin analogues and vasopressin V_2-receptor antagonists (V2RA),

have shown promising results.[7-9] The clinical trials testing mTOR inhibitors showed no clear impact on disease progression.[10-12] However recent results from the TEMPO 3:4 and ALADIN trials with the V2RA Tolvaptan and the somatostatin analogue Octreotide have shown an effect on the rates of kidney growth and kidney function decline, although long term treatment safety needs to be addressed.[13,14] If these therapies become available for clinical use, the pivotal question will be which patients to select for treatment. One can hypothesize that ADPKD patients with rapid disease progression would benefit most and that treatment should be started at an early stage of disease, when the kidneys are more likely to respond to an intervention. Since ADPKD is characterized by a long period of stable kidney function, due to compensatory filtration of unaffected nephrons, kidney function does not accurately reflect disease severity nor prognosis.[15] Genotype (PKD1 as opposed to PKD2 mutation), male gender and young age at onset of hypertension among others associate with faster disease progression in ADPKD.[16,17] However, the predictive value of these variables is limited and untested in large prospective cohorts. The identification of surrogate markers to assess disease severity and risk of progression and to monitor the effect of interventions on the course of disease remains an important goal and is an unmet medical need. Results of smaller observational studies in ADPKD cohorts, like CRISP and SUISSE ADPKD, suggest that changes in total kidney volume are a predictor of subsequent loss of kidney function.[18] MRI has a greater sensitivity for the detection of small cysts and allows to measure kidney and liver volume more precisely compared to ultrasound. It has been shown that MRI can already reliably detect changes in total kidney volume that occur during 6 months of follow-up.[19] However, the two interventional trials with mTOR inhibitors (references 10 and 11) did not observe a correlation between total renal volume and disease progression (as measured by renal function) questioning whether total kidney volume is a suitable surrogate marker for disease progression. In addition, this imaging technique is not routine clinical practice for ADPKD subjects in all European countries. Thus, there is a need to discover clinical factors or new biomarkers that predict the rate of disease progression.

Building a large, well-characterized cohort of ADPKD subjects who are followed in a longitudinal observational cohort study has the potential to identify progression factors and biomarkers, and to assess disease stage specific mortality, morbidity and health care costs. This knowledge should translate into new diagnostic and therapeutic modalities. This approach requires a coordinated multinational action within a network of ADPKD reference centers. The EuroCYST Initiative aims to build such a network and to establish a large-scale pan-European ADPKD cohort serving as a versatile and powerful clinical research platform. Since EuroCYST is an academic initiative and not industry driven, free access to information and pseudo-anonymized biomaterial is ensured, as approved by a research oversight committee.

Methods

Objectives

The primary objectives of the EuroCYST Initiative are to:

- Build a network of ADPKD reference centers across Europe to provide a translational research platform that will enable EU researchers to study the pathogenesis, progression factors, morbidity, co-morbidity and health economic issues in ADPKD patients over a wide range of kidney function and kidney volume.
- Harmonize and develop common standards for ADPKD related research by a collaborative effort to establish a pan-European ADPKD cohort.
- Harmonize and develop a common ADPKD biobank that includes standardized, quality-controlled biomaterials for translational research.
- Create a scaffold to facilitate the integration of current and upcoming technologies to ADPKD practice.
- Develop evidence-based best practice and needs assessments for ADPKD by utilizing the outcomes of the EuroCYST Initiative and by engaging with relevant stakeholders, including patient organizations, clinical and research networks, legislators, policymakers and the pharmaceutical industry.
- Serve as an impetus to expand ADPKD training programs at all levels by establishing collaborative and educational liaisons as well as provide standard criteria for effective management protocols in ADPKD.
- Improve awareness of the relevance of ADPKD including disease-specific complications and socioeconomic consequences of the disease among health care professionals and payers.

EuroCYST strategy and organization

To build a cohort for a longitudinal observational study, 14 centers in 10 countries across Europe (Figure 1) will enroll 1,100 adult ADPKD patients until the end of 2015. The study is funded by a grant of the ERA-EDTA with 1 Million Euros. For optimal utilization of the funding, centers with expertise in ADPKD and already existing local clinical cohorts have been co-opted, so that efforts do not need to focus on recruitment, but can be invested into the establishment of the cohort infrastructure, uniform data recording and in depth analysis of several time and thus resource-consuming aspects, such as assisted patient interviews using standardized questionnaires.

The enrollment phase started in summer 2013; within one year, 250 participants should be included. In order to reach the goal of recruiting 1,100 ADPKD patients, each participating ADPKD center will enroll at least 50 and up to a maximum of 100 patients within two years to ensure a representative distribution of patients across Europe. In a second step, which is beyond the current funding period, the cohort could be extended in four ways: a) prolong the intended duration of follow-up to longer than three years, b) increase the number of patients up to 5,000 or more through the participation of additional European study centers with a minimum essential dataset, c) increase the information density per patient for specific aspects (e.g. cardio-vascular pathology, imaging, genetics), or d) enroll partners, children and parents of index patients (3-generation cohort). The participation of additional centers will be possible if appropriate funding is obtained. Collaborations at various levels with other research groups to share data and biomaterials in order to achieve maximum scientific output will be encouraged. To this end an open and transparent ancillary study policy has been established as part of the study protocol (Supplement S1).

A Steering Committee has been established and is meeting at least twice a year. All decisions by the Steering Committee will be approved on a 75% majority. The establishment

of a Central Study Coordination Team, which meets on a bi-weekly basis, will ensure rapid and successful project implementation and progress.

Eligibility of cohort participants

Following a consecutive enrollment approach all patients with ADPKD are considered as potentially eligible for the study at pre-screening and will undergo screening for the study. Patients aged 18 years and older with an estimated GFR (eGFR) of 30 ml/min/1.73m^2 and higher (CKD-EPI formula), having a diagnosis of ADPKD established based on kidney ultrasound and family history (modified Ravine criteria) who have not taken part in a disease modifying trial at least one year or shorter before enrollment and are able to provide written informed consent will be eligible for enrollment into the EuroCYST cohort.[20,21] Table 1 displays the inclusion and exclusion criteria. Exclusion criteria include the likelihood of reaching ESRD within one year after enrollment or significant heart disease according to New York Heart Association stage IV (NYHA stage IV).[22] A stratification strategy based on subjects eGFR will avoid selection bias. Each study center will enroll 40 to 60% of patients with eGFR greater or equal and under 60 ml/min*1.73m^2 respectively.

Study design

Patients who meet the inclusion criteria will be invited to participate. All potential participants will receive detailed information about the study both verbally and in writing. Local ethical committees will approve the study and the protocol has to fulfill the local regulatory requirements and complies with Good Clinical Practice Guidelines (GCP).

The study design is shown in Figure 2. At baseline a detailed medical and ADPKD-specific assessment will be performed. Family history/pedigree information will be collected,

as well as information on medical resource use (health care visits, hospital admission, procedures, and medication), productivity (employment, absenteeism), information culture within families and reproductive planning. The economic and social position, based on income, education, and occupation will be assessed. Quality of life will be measured by asking patients to complete the KDQOL-SF 1.2™ questionnaire, that includes questions relating to patients general health, kidney disease and about the effect of the disease on activities of daily living. The protocol will also require a physical examination.

Follow-up visits will be conducted on an annual basis until the end of study, withdrawal, ESRD or death. Follow-up visits will include physical examination; laboratory analyses as well as completing the aforementioned ADPKD related questionnaires. Participating patients will be treated according to current standards of care in routine clinical practice within each country.

Magnetic resonance imaging

MRI will be used to measure the different magnitudes and volume parameters of kidney and liver. MRI will be performed at the baseline visit and is recommended at 3-year follow-up. In order to obtain high quality renal and hepatic imaging and maintain consistency between the centers participating in the trial, a standardized protocol has been developed. The MRI acquisition protocol includes T2 single shot fast/turbo spin echo images with fat-saturation, FISP or FIESTA 3D spoiled gradient echo, and T1-3D spoiled gradient echo. Images will be sent using Picture Archiving and Communication System (PACS) to the centers Zurich and Bergamo, where a read out by trained personnel will be performed. Read out of the scans includes whole kidney and cyst volume, length, depth, width of the kidney, numbers of cysts, and also liver and liver cyst volume, using the workstation GE Advantage and the program volume viewer.

Collection and storage of biological material

The collection of material for biobanking will be conducted at the baseline visit. A Standard Operating Procedure (SOP) harmonizes the procedure for sampling, pre-processing and storage of biobanking material within the EuroCYST Initiative. Serum, plasma and whole blood collected on EDTA and spot and 24 h urines will be collected, processed and aliquoted. They will be shipped in batches to a central biobank storage facility where an automated -80°C sample library management system is in place to handle the de-identified 2D bar coded sample vials. The whole blood tubes will be shipped to a central, certified genetic laboratory for DNA extraction and storage. The database will be kept separately with a secure method to link clinical information to biological samples.

Data management and protection

Data collection and data management will be conducted using the web-based data management system SecuTrial®, with a data capture, which has been approved by the US Food and Drug Administration (FDA) and that fulfills the requirements of the International Conference on Harmonization Good Clinical Practice (ICH GCP) and Good Clinical Data Management Practices (GCDMP). All electronic case report forms (eCRF) have been implemented into this system. Figure 3 shows the different subject areas of the data bank that are reflected in the eCRF. Data will be stored for at least 10 years after study termination and a daily back up will be performed. The study data are saved on a separate server at the University Hospital Zurich, where the clinical trial center, provider of the data management system, is located. Server access is controlled physically and electronically. Each patient will be pseudo-anonymized in a reversible manner and all data introduced into the data management system is coded. Subject identification will only be possible at the local study site. Access to the system will be role specific and will only be possible with a unique User-

ID and password. High data quality will be ensured by performing regular monitoring and reporting of entered data by the coordination center Zurich. All study site data entered in the eCRF will be checked for completeness and plausibility according to predefined rules to draw attention to missing data or errors. Certified personnel will monitor the participating center annually. All patients' written informed consent forms and all study files will be checked for completeness, and remain at the individual sites. In 10% of locally enrolled patients, the source files and eCRFs will be checked for accuracy. In addition, frequent communications and annual meetings of reference center principal investigators will ensure study compliance. The center's individual results of the study shall be owned by the center. Each center will provide copies of all results, including but not limited to case report forms, to the study coordination center in Zurich. Owner of the overall data of the Initiative is the EuroCYST steering committee.

Statistical considerations

Formal sample size estimation has not been performed for this study. While chronic kidney disease cohorts currently aim to enroll at least 3,000 and up to 5,000 patients (CRIC, CKD JAC, GCKD) to identify valid associations in subgroups, the common genetic origin in APDKD allows important conclusions to be drawn using a smaller sample size.[23-25] On the other hand, groups of several hundred patients enrolled in recent randomized controlled trials (RCTs) as well as already existing ADPKD cohorts have displayed large variability in the disease progression rate as assessed by the change in eGFR rate and total kidney volume (TKV) despite restrictive inclusion and exclusion criteria. Therefore a larger sample size is required to account for the broader range in age and renal function in our cohort. A mixed effects regression model will be used as the modeling framework, with a random effect for each patient (this allows correlation between repeated eGFR or TKV measurements in the

same patient) and with fixed effects for time with a spline structure to model change in estimated GFR and TKV.

Study outcomes

The primary outcome measure of the study will be disease progression, assessed as change in eGFR (CKD-EPI) and change in TKV. Secondary outcome measure will be: firstly, onset and severity of ADPKD-related clinical outcomes, such as hypertension, albuminuria, renal urine concentrating ability, hematuria, renal pain, cyst infection and nephrolithiasis; secondly, self-reported health status, quality of life and pain; thirdly, health related resource use and ADPKD-related health burden.

Enrollment Start

The study started enrolling patients in July 2013 and will run for 36 months.

Conclusion

The fragmentation of cohorts of ADPKD patients in Europe has been an obstacle to a better understanding of disease characteristics. Individual efforts in different countries often have little inter-changeability and it can be almost impossible to connect detailed clinical information held in one database with genetic information or biomaterial sample availability held in other databases. Our increasing knowledge of the basic biology of ADPKD has led to the identification of multiple novel targets in pre-clinical studies, which will need to be tested in patients. Positive results from recent clinical trials also now compel nephrologists to find new ways of risk stratification to identify patients at higher risk of disease progression and who may benefit most from early intervention. So far, limited data is available addressing patients' quality of life, disease related health burden, health care resource use and reproductive planning. Currently available data regarding quality of life for ADPKD patients is limited and often only applicable to those on dialysis or transplanted patients.[26-29]

These issues motivated the EuroCYST Initiative, which aims to build an ADPKD reference center network in Europe in order to establish a large pan-European observational cohort that will serve as a scaffold and platform enabling researchers to study the pathogenesis, progression factors, mortality, co-morbidity, as well as health economic issues relevant to ADPKD as a major cause of kidney disease. Although there is an interest of the pharmaceutical industry to establish ADPKD databases, an independent academic network with a transparent open access policy remains essential. The recent establishment of the ERA-EDTA Working Group on Inherited Kidney Disorders demonstrates the interest and need for a consolidated pan-European approach in the field of inherited kidney diseases at large.[30]

The establishment of such a cohort has the potential to strengthen European ADPKD investigators by harmonizing and standardizing research efforts and will guarantee that current and upcoming technologies to study chronic kidney disease can be applied to ADPKD

patients across Europe. Affected patients and their relatives will benefit from the scientific-medical innovations by improved prevention and awareness, treatment of disease-specific complications and development of new diagnostic and therapeutic modalities.

Acknowledgements

This study is supported by a grant of the ERA-EDTA.

Disclosure

The authors declare no conflict of interest.

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Figures

Figure 1. Location of participating study sites in the EuroCYST Initiative

Figure 2. Study Design

Figure 3. Content of the Databank

Tables

Table 1. In- and exclusion criteria for the EuroCYST observational cohort study.

Inclusion criteria
• Age ≥ 18
• eGFR ≥ 30 ml/min/1.73m^2 (CKD-EPI formula)
• Clinical diagnosis of ADPKD based on kidney imaging and family history (modified Ravine criteria)
• Patient provided written informed consent
Exclusion criteria
• Receiving chronic renal replacement therapy before enrollment (dialysis, allograft) or anticipated to receive such therapy within 12 months after enrollment
• Participation in a clinical trial aiming to modify disease outcome one year or less before enrollment in the EuroCYST study
• NYHA stadium IV

Abbreviations: eGFR – estimated glomerular filtration rate, NYHA – New York Heart Association

Supplements.

SI. Study Protocol

Appendix.

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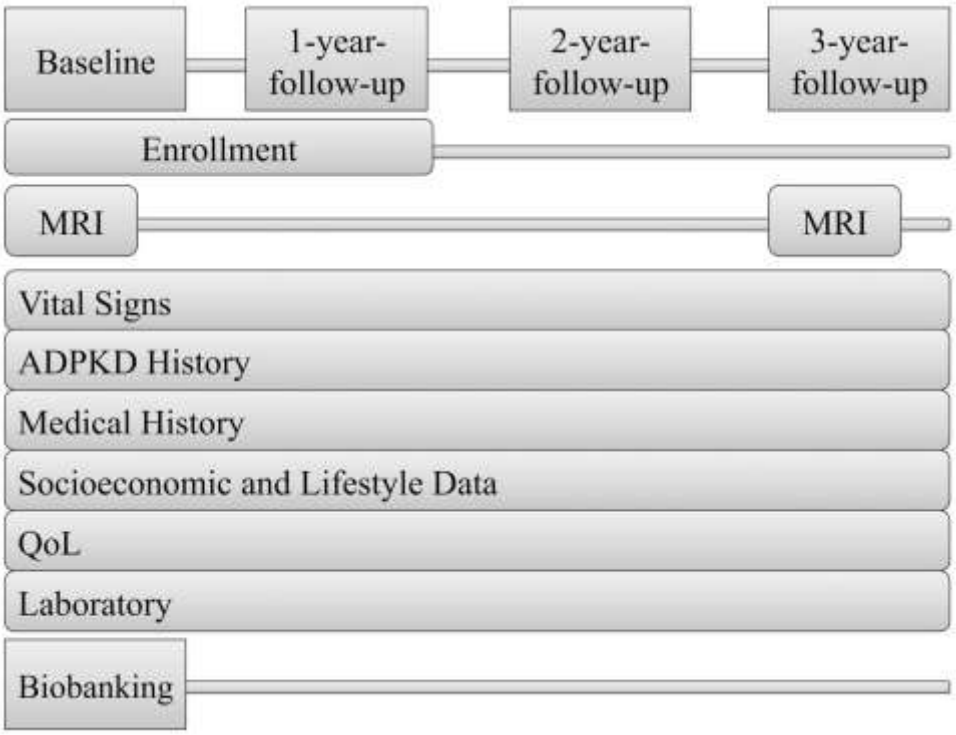
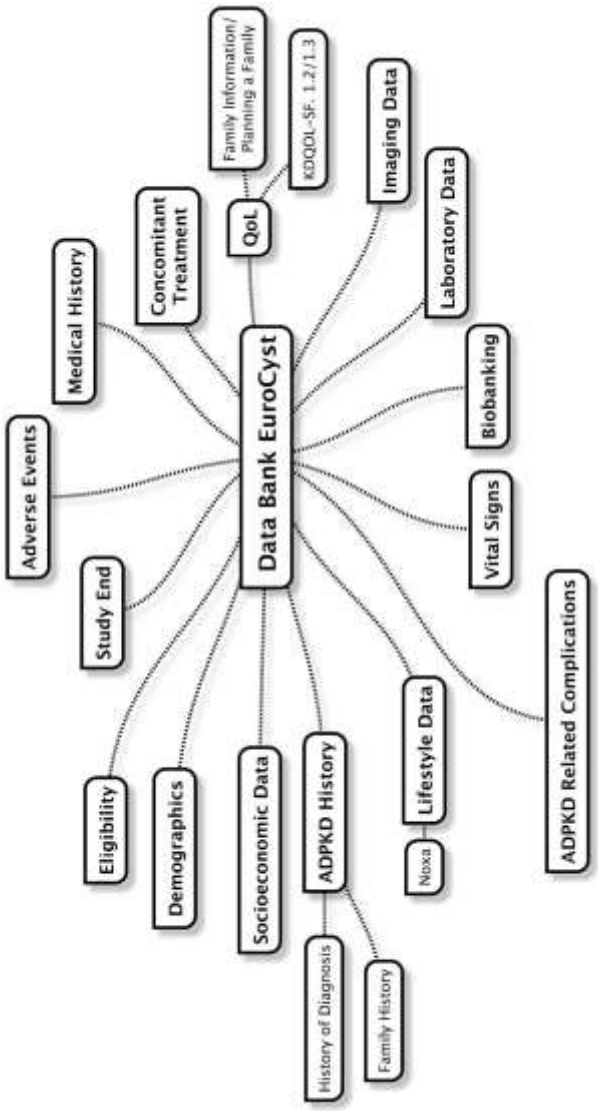
Location of participating study sites in the EuroCYST Initiative
83x59mm (600 x 600 DPI)



Study Design
89x67mm (600 x 600 DPI)



Content of Databank
138x241mm (600 x 600 DPI)

Manuscript: Building a network of ADPKD Reference Centers across Europe: The EuroCYST Initiative (NDT-00126-2014)

Point by point answers to review NDT (February 4th, 2014)

1. This cohort study risks to induce a substantial selection bias towards "more serious disease", first because only patients with advanced disease will be identified (because of symptoms), and not those with asymptomatic disease, and second because it can be imagined that only those with more advanced disease will be motivated to participate. This aspect is completely neglected in the paper, and should be discussed.

We agree with reviewers' comment that there might be a risk of enrolling a majority of patients with more advanced disease. In the EuroCYST study we recruit patient from a hospital setting. The cohort should reflect the range of outpatient cases. In the EuroCYST study, we might induce a study limitation because of a selection bias, in our case particularly a sampling bias. With choosing the hospital setting, we might risk to enroll a majority of patients with advanced disease progression. This limitation could lead to an over-representation of more patients with serious disease. For reducing the risk of a sampling bias, we propose the following approach: A stratification per study center of 40 to 60% of enrolled patients with eGFR greater or equal than 60 ml/min*1.73m^2.

1.1 In the same line of reasoning the percentages of patients ending up on RRT is not really known, is as suggested in line 24 pg 7

We adapted the paragraph as follows: "Kidney function is often preserved up to the age of 40, but subsequently glomerular filtration rate (GFR) decreases, and often leading to end-stage renal disease (ESRD) between the 4th and 7th decade of life.[3]"

2. Line 4-6 page 8: the results of the TEMPO trial are being presented here as "promising"; however, to my knowledge, the impact on effect size was minimal, and there was serious concern on hepatotoxicity of the drug. Most nephrologists would not consider the result of this study as "promising". This statement should be at least made more balanced, or be removed.

We agree to reviewers' opinion and modified the paragraph to "…The clinical trials testing mTOR inhibitors showed no clear impact on disease progression.[10-12] However recent results from the TEMPO 3:4 and ALADIN trials with the V2RA Tolvaptan and the somatostatin analogue Octreotide have shown an effect on the rates of kidney growth and kidney function decline, despite the fact the that safety issues of a long term treatment need to be addressed.[13,14] …"

3. Line 38-39 page 8: again, the enthusiasm about changes in kidney size in relation to progression is a bit exaggerated; associations with renal function and evolution to RRT are in fact weak, especially in the lower, non caricatural range of kidney volume. There is at least much debate on the real value of kidney volume as surrogate marker. This paragraph should be made more balanced.

In response to the reviewers' opinion we modified the paragraph into "…Results of smaller observational studies in ADPKD cohorts, like CRISP and SUISSE ADPKD, suggest that changes in total kidney volume are a predictor of subsequent loss of kidney function.[18]…"

4. Line 17-21 of page 9: it is stated that the group acts independent from industry; however, the majority of authors of this paper clearly have ties with industry, and have participated in an industry sponsored RCT on this topic, and many of them probably receive industry money for their research; it is therefore strange that only one conflict of interest is declared. This is not really credible.

The present research project is academic, independent of industry and solely funded by the ERA-EDTA. All authors declare no conflict of interest. The COI form of the lead author will be submitted.

4.1 In the same line: it is stated that 14 centres will participate: how were these centres selected?
Centers with expertise in ADPKD research have been selected, so that efforts do not need to focus on recruitment, but can be invested into the establishment of the cohort infrastructure, uniform data recording and time- and thus resource-consuming aspects, such as assisted patient interviews using standardized questionnaires.

4.2 Who made this selection?
The selection of the participating center was made by the Steering Committee of the EuroCYST Initiative.
The members of the Steering Committee are:

Prof. Dr. Olivier Devuyst (University Zurich)
Prof. Dr. Kai-Uwe Eckardt (University Hospital Erlangen)
Dr. Ron Gansevoort (University Medical Center Groningen)
Prof. Dr. Albert Ong (University of Sheffield)
Prof. Dr Yves Pirson (Clinique universitaire Saint Luc Brussel)
Prof. Dr. Giuseppe Remuzzi (IRCCS – Instituto di Ricerche Farmacologiche Mario Negri Bergamo)
Prof. Dr. Richard Sandford (University of Cambridge)
PD Dr. Andreas Serra (University Hospital Zurich)
Prof. Dr. Gerd Walz (University Hospital Freiburg)

4.3 Is there any evidence to support that these centres are representative of "regular centres" and that their patients are representative of "regular" patients?
The centers that participate in this initiative are not regular centers, but centers with expertise in ADPKD research. We have changed the text of the manuscript to reflect this consideration. As the reviewer will know the rate of disease progression in ADPKD is characterized by a wide variability, even between pedigrees that share the same mutation in either of the PKD genes. So far it is therefore not possible to describe the "regular" ADPKD patient. The EuroCYST Initiative, pursuing a multinational approach, aims to address this issue.

5. Recruitment process: how will this be done?
Since all participating center have already established local cohorts with systematic data available, the recruitment of patients is arranged.

5.1 Is there any regulation to assure consecutive rather than selective enrollment of ADPKD patients?
We propose consecutive enrollment of study subjects. Consecutive enrollment is a measure to prevent selection bias and we think that consecutive enrollment is important since observational studies are always compromised for selection bias that subsequently can't be addressed by any statistical approaches. Following a consecutive enrollment approach means that all ADPKD patients are considered as potentially eligible for the study at pre-screening and will undergo screening for EuroCYST. The screening process starts with the signature of the IC. All patients that fulfill our defined inclusion criteria, do not fulfill any of the exclusion criteria and provided written informed consent are considered for enrollment. Those who do not meet all the inclusion or do meet one or more of the exclusion criteria will be considered as screening failures and will not be enrolled in the study. For reducing the risk of a sampling bias, we propose the following approach: A stratification per study center of at least 40% of enrolled patients with eGFR greater or equal than 60 ml/min*1.73m^2.

5.2 Nothing is stated about the fact whether these will be "incident" or "prevalent" patients, whereas this would however have a severe impact on the later analysis of the data.
According to our study design the recruited patients will be predominantly prevalent patients. Since ADPKD is a genetic disorder for which there is no effective treatment available yet, we expect no difference between incident and prevalent patients with respect to the rate of disease progression. In addition, the time after diagnosis will be recorded in the database, which can be used for later analysis of data.

6. Line 35, page 11: "To this end an open and transparent ancillary study policy has been established" can authors specify where this "transparent" study policy can be found?
Ancilllary studies will be evaluated by the Steering Committee and decision making is based on 3/4 vote. This ancillary study policy is described in the study protocol that has been added as supplementary material to the manuscript (S1).

6.1 Has the study protocol in full been posted and published? If yes, the place where the reader can find this information should be provided; if no, the current paper should be reformatted to comply with the STROBE regulations (http://www.strobe-statement.org/)
The study protocol hasn't been posted or published so far. We have therefore added the study protocol in the supplement of this manuscript. A reference to this supplementary material has been incorporated in the revised version of the manuscript (EuroCYST strategy and organization).

7. Who will pay for the MRI and the additional lab costs?
Each center will receive a predefined amount of money per enrolled patient per visit. The amount of money paid for the baseline visit, that includes a mandatory MRI, covers the costs for imaging as well as additional lab costs. Due to the limited amount of money the second MRI, that should take place at third year visit, is not mandatory, but highly recommended.

8. Who will own the data?
The center's individual results of the study shall be owned by the center. Each center will provide copies of all results (including but not limited to CRF's) to the study coordination center in Zurich. Owner of the overall data of the Initiative is the EuroCYST steering committee. This information has been added to the manuscript (paragraph: Data management and protection)

8.1 Where will the data physically be stored?
The study data are saved on a separate server at the University Hospital Zurich, where the clinical trial center, provider of the data management system, is located. Server access is controlled physically and electronically. A daily backup will be performed. This information has been added to the manuscript (paragraph: Data management and protection).

8.2 Who has access to the data?
Each center has defined a number of study members that have access to the data management system. The access to the system is personal, role specific and secured with a password. Each center will have access to its own data. The coordination center Zurich will have access to all data that are stored in the central data management system. Individual participating centers, as well as third parties, may ask for datasets by submitting proposals for ancillary studies.

9. Who has funded this study? This is not clear from the paper
The study is funded by a grant of the European Renal Association – European Dialysis and Transplantation Association (ERA-EDTA) with 1 Million Euro. We added this information to the manuscript under EuroCYST strategy and organization.